IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# REVOLUTIONIZING TRANSDERMAL DELIVERY: UNVEILING THE POTENTIAL OF MICRONEEDLE TECHNOLOGY

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**Abstract:**

Transdermal drug delivery offers abundant advantages, including bypassing hepatic first-pass metabolism and ensuring steady plasma concentrations, enhancing safety, and promoting patient compliance. However, the major obstacle lies in the limited number of potent drugs with suitable physicochemical properties capable of effectively permeating through skin barriers via passive diffusion. To overcome this challenge, various strategies have been explored, with micro needles emerging as a promising micro scale physical enhancement method. Typically ranging from 0.1 to 1 mm in length, micro needles significantly widen the range of drugs feasible for transdermal and intradermal delivery. This review examines micro needle materials, fabrication techniques, characterization methods, and their applications in transdermal drug delivery. Despite extensive discussion on their implications, challenges persist in achieving sustained delivery, ensuring efficacy, and optimizing cost-effective large-scale manufacturing. Furthermore, this review explores the potential impact of micro needles on drug delivery, vaccine administration, disease diagnostics, and cosmetic applications. Overall, micro needles hold promise as a versatile tool in transdermal delivery systems, although further advancements are needed to overcome existing limitations and fully realize their potential across diverse applications.

**Keywords**: Transdermal drug delivery, Microneedle, advanced manufacturing, polymers, therapeutics.

## ➢ INTRODUCTION

The transdermal route of drug delivery is presented as an appealing, non-invasive method for drug administration. Drugs administered via this route exhibit high bioavailability as gastrointestinal degradation and first-pass metabolism are bypassed. (1) During transdermal permeation, drugs accumulate in the skin before release into the bloodstream, facilitating naturally sustained drug delivery. Despite its numerous advantages, transdermal drug delivery is restricted to molecules with specific physicochemical properties (2) .

Ideally, transdermal candidates should have a molecular weight less than 500 Da and a log P within the range of 2–3. (3)

The stratum corneum acts as the primary barrier for transdermal permeation (4). Several technologies have been developed to disrupt the stratum corneum to enhance skin permeability, including iontophoresis, sonophoretic, magnetophoresis, electroporation, and laser-micro oration (5). However, these methods have significant applicability and economic limitations. Traditional drug delivery systems like intradermal injections are currently used to address the challenges associated with transdermal delivery. Nevertheless, intradermal injections are hindered by issues such as needle injuries, patient phobia, and the need for specialized staff, thereby increasing delivery costs(6).

Micro needle drug delivery presents a solution to the limitations posed by traditional dosage forms. This technology has been demonstrated to deliver not only small molecules but also various macromolecules, cosmeceuticals, and micro/Nano-particles.

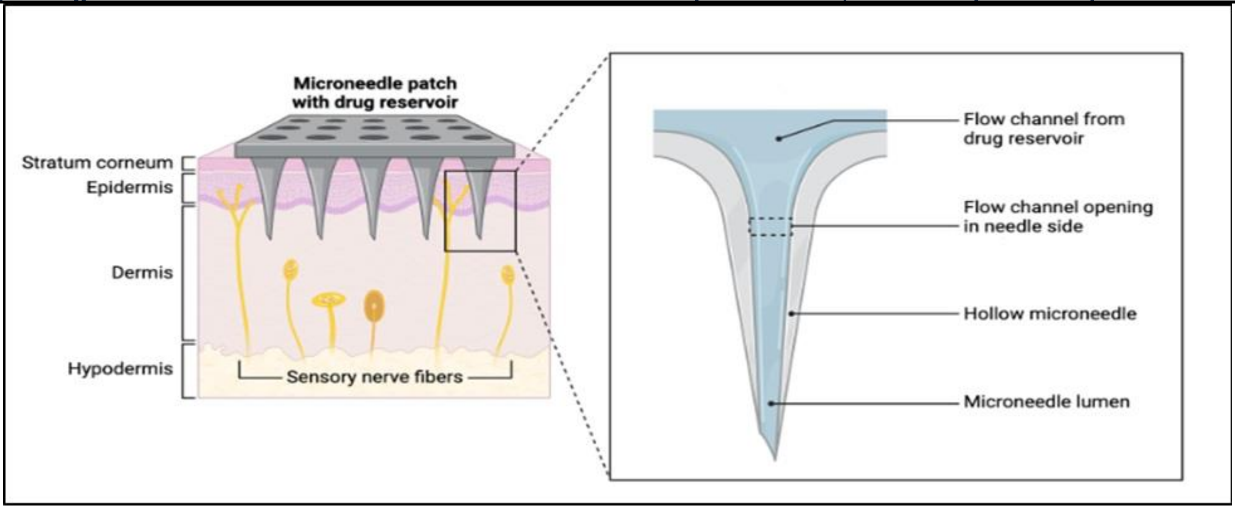


**figure: 1 transdermal micro needle structure and permeation through layers of skin**

Recently, coated and dissolving microneedles have been explored for non-invasive transdermal vaccination, patient monitoring, and diagnostic applications. Research and development of microneedles have progressed to the stage of large-scale manufacturing and commercialization. Microneedles have not only been investigated for transdermal drug delivery but also find utility in ocular, diagnostic testing, and oral delivery (7).

This review highlights micro needling as a promising approach for bypassing the stratum corneum to enhance transdermal drug delivery. Microneedles, tiny needling systems, create painless micro-channels in the skin, allowing therapeutic agents to diffuse into the well-perfused dermal layer (8). Their length varies to ensure epidermal penetration without nerve fiber stimulation or blood capillary puncturing. Unlike conventional injectables, microneedle delivery isn't limited by molecular size due to larger channels.

Various micro fabrication techniques produce micro needles of different materials, geometries, and dimensions (height: 50-900 µm, surface area: 2000 mm^2) (9). regulatory concerns and explores various critical aspects of microneedle technology, encompassing types, materials, geometries, penetration depth, drug release mechanisms, and the potential for irritation.(Refer figure 1)

- **Features of Micro needle's (MN'S)**

Below image shows the advantages of microneedle in transdermal drug delivery.

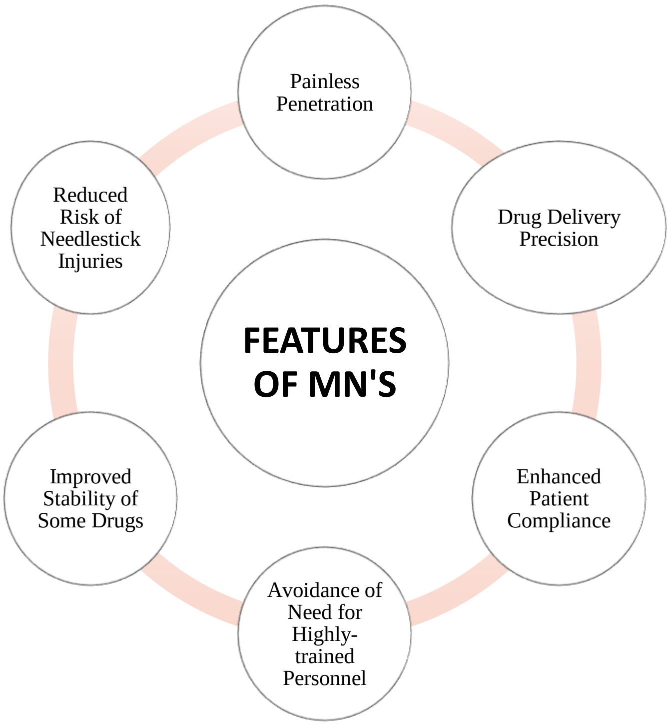


**figure: 2 features of micro needle's (mn's)**

## ➢ Types of Micro needle's

Micro needles are categorized based on their fabrication strategy into two groups: in-plane and out-of-plane Micro needles. They are further classified into solid, hollow, coated, dissolving, and Bio-responsive types, depending on their specific drug delivery mechanisms and characteristics (10).

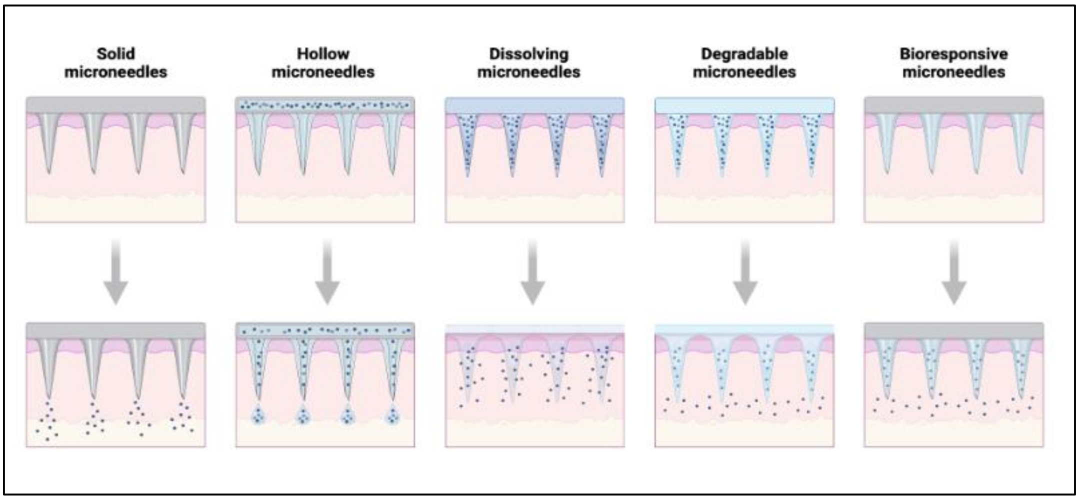


**figure: 3 delivery mechanisms through different types of micro needle patches**

Microneedles can be classified (11) into several types based on their design, structure, and functionality:

**1. Solid Microneedles**: These are solid structures typically made of materials like silicon, metal, or polymers (12). They create microchannels in the skin to facilitate drug delivery without the need for any additional mechanisms .

**2. Hollow Microneedles**: These have a hollow core that allows for the direct delivery of drugs or substances through the needles into the skin (13).They can be used for various applications, including injections and sampling (14).

**3. Coated Microneedles**: These have a coating on the surface that contains the drug or active ingredient (15). The coating dissolves or dissolves upon insertion into the skin, releasing the drug into the targeted tissue (16).

**4. Dissolving Microneedles:** These are made of materials that dissolve upon insertion into the skin, releasing the encapsulated drug or substance into the tissue (17). They offer a painless and convenient method of drug delivery.

**5. Hydrogel-Forming Microneedles:** These are designed to swell and form a hydrogel upon insertion into the skin (18). The hydrogel matrix can encapsulate drugs or active ingredients, providing sustained release and controlled delivery over time.

**6. Bio-responsive microneedles**: These are an innovative drug delivery system that responds to specific biological signals or conditions in the body, offering targeted and precise delivery of therapeutic agents based on the body's needs (19).

## ➢ Materials used for preparation of Microneedle

Microneedles can be fabricated from a variety of materials, each offering different properties and advantages for specific applications. Some common materials used for microneedles include (20),(21)

I. Silicon: Silicon microneedles are durable, biocompatible, and can be fabricated with precise dimensions. They are often used for applications requiring high mechanical strength and precision, such as transdermal drug delivery and minimally invasive diagnostics.

II. Metals (such as stainless steel, titanium, and gold): Metal microneedles offer excellent mechanical strength and conductivity, making them suitable for applications such as drug delivery, electrochemical sensing, and sampling.

III. Polymers (such as polydimethylsiloxane (PDMS), polylactic acid (PLA), polyglycolic acid (PGA), and polylactic-co-glycolic acid (PLGA)): Polymer microneedles are flexible, biodegradable, and can be tailored to degrade or dissolve in the body, making them suitable for applications requiring controlled drug release and minimally invasive procedures (22).

IV. Hydrogels: Hydrogel microneedles swell and soften upon insertion into the skin, enhancing patient comfort and drug delivery efficiency. They are often used for applications requiring sustained release and localized delivery of drugs or biomolecules.

V. Ceramic materials: Ceramic microneedles offer unique properties such as high temperature resistance and biocompatibility, making them suitable for applications in harsh environments or specialized medical procedures.

The choice of material for microneedle fabrication depends on factors such as the intended application, desired mechanical properties, biocompatibility, and degradation characteristics.

➢ **Method for Microneedle**

Several methods are used for the formation of microneedles, each offering unique advantages in terms of fabrication precision, scalability, and material compatibility. Some common methods include (23)

1) **Micromolding**: Micromolding involves casting a material (typically a polymer) into a mold with microneedle-shaped cavities and then solidifying the material to form microneedles (24) . This method is suitable for large-scale production and allows for precise control over microneedle dimensions and geometry .

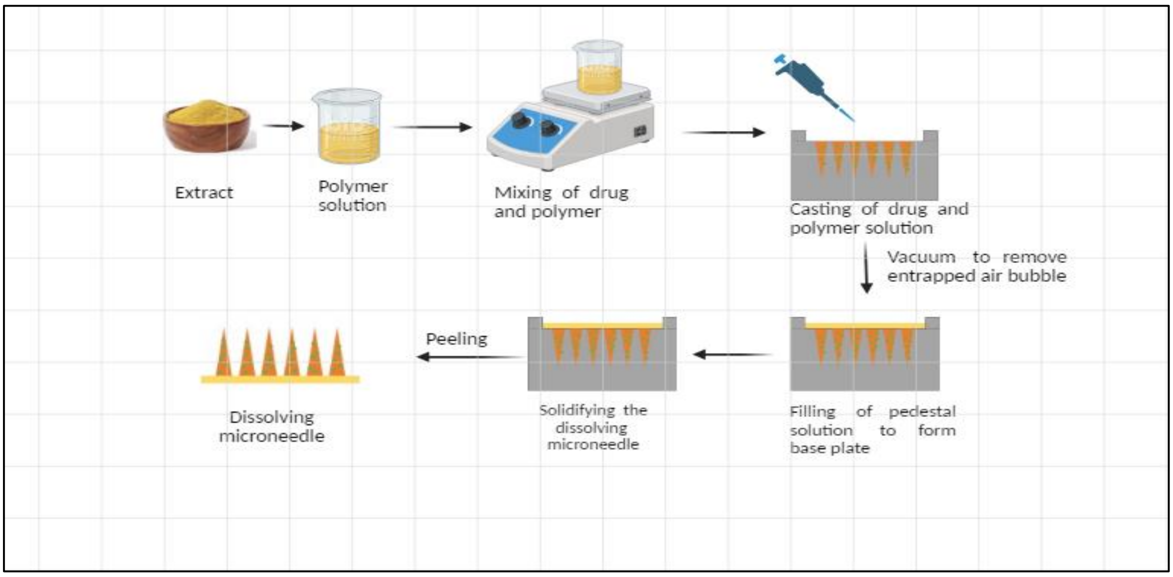


**figure: 4 schematic diagram micromolding method**

Basic steps involve for micromolding method

- Design of Microneedle Mold: Design a microneedle mold with the desired microneedle geometry and dimensions. The mold can be fabricated using techniques such as photolithography, micromachining, or 3D printing.
- Material Selection: Choose a biocompatible polymer or material suitable for microneedle fabrication. Common materials include polymeric substances like polydimethylsiloxane (PDMS), polyethylene glycol (PEG), or polylactic-co-glycolic acid (PLGA).
- Preparation of Polymer Solution: Prepare a polymer solution by dissolving the chosen polymer or material in a suitable solvent. The solvent should be compatible with the polymer and allow for easy molding and removal of air bubbles.
- Micromolding Process:
  - ❖ Pour the polymer solution onto the microneedle mold, ensuring even distribution to fill the mold cavities completely.
  - ❖ Apply vacuum or pressure to remove any air bubbles trapped in the polymer solution.
  - ❖ Cure or solidify the polymer solution using methods such as heating, UV exposure, or chemical cross-linking. This step ensures that the polymer retains the shape of the microneedle mold.
- Demolding: Once the polymer has solidified, carefully remove the microneedle array from the mold. Handle the microneedle array with care to avoid damage to the delicate structures.
- Post-processing (Optional): Perform any necessary post-processing steps, such as trimming excess material or surface modification, to refine the microneedle array and enhance its properties for specific applications.

  The micromolding method offers precision and scalability in microneedle fabrication, allowing for the production of microneedle arrays with uniform dimensions and high reproducibility. However, it is essential to optimize parameters such as polymer concentration, solvent selection, and molding conditions to achieve the desired microneedle characteristics and performance.

2) **Photolithography**: Photolithography uses light to transfer a microneedle pattern onto a substrate coated with a light-sensitive material (photoresist). After exposure to light through a mask, the photoresist is developed to create a microneedle pattern on the substrate (25). This method enables precise control over microneedle dimensions and allows for high-throughput fabrication.

3) **Laser ablation**: Laser ablation involves using a laser to selectively remove material from a substrate, creating microneedle structures. This method offers high precision and flexibility in microneedle design and can be used with a wide range of materials, including polymers, metals, and ceramics.
4) **3D printing:** 3D printing, also known as additive manufacturing, builds microneedle structures layer by layer using computer-controlled deposition of materials such as polymers, metals, or ceramics (26). This method allows for rapid prototyping and customization of microneedle designs and is suitable for producing complex geometries.
5) **Drawing lithography**: Drawing lithography involves pulling microneedles from a heated polymer solution using a micropipette or capillary (27). This method is simple and cost-effective and allows for the fabrication of microneedles with fine tips and precise dimensions.
6) **Electrochemical etching**: Electrochemical etching involves using an electric current to selectively dissolve metal substrates and create microneedle structures (28). This method offers high precision and control over microneedle dimensions and is commonly used for fabricating metal microneedles.

These methods can be used alone or in combination to fabricate microneedles with various shapes, sizes, and materials, catering to specific applications in drug delivery, diagnostics, and biomedical research.

➢ **Application of Microneedles**

Microneedles have a wide range of applications across various fields, including medicine, pharmaceuticals, diagnostics, and biotechnology. Some key applications of microneedles include (29) (30) (31) (32) (33) (34) (35):

1) Transdermal Drug Delivery: Microneedles enable painless and non-invasive delivery of drugs and therapeutics through the skin. They can bypass the skin's barrier function and deliver drugs directly to the underlying tissue, providing a more efficient and targeted approach compared to traditional oral or injectable delivery methods. Microneedles are used for delivering a variety of drugs, including small molecules, peptides, vaccines, and biologics.
2) Vaccination: Microneedle-based vaccine delivery offers several advantages, including improved patient compliance, enhanced immune response, and dose sparing. Microneedle patches coated with vaccine antigens can be painlessly applied to the skin, where they dissolve or release the vaccine into the skin's immune-rich environment, eliciting a robust immune response.
3) Continuous Glucose Monitoring: Microneedle-based sensors can be used for continuous monitoring of glucose levels in diabetic patients. These sensors penetrate the skin painlessly and measure glucose concentrations in the interstitial fluid, providing real-time data for managing diabetes and optimizing insulin therapy.
4) Diagnostics: Microneedles can be integrated with biosensors or microfluidic systems to create minimally invasive diagnostic devices. Microneedle-based biosensors can detect biomarkers, proteins, or nucleic acids in bodily fluids such as blood, saliva, or interstitial fluid, enabling rapid and sensitive diagnosis of various diseases and conditions.
5) Cosmetics and Dermatology: Microneedles are used in cosmetic and dermatological applications for skin rejuvenation, scar reduction, and delivery of skincare ingredients. Microneedle-based patches or rollers create microchannels in the skin, allowing for improved penetration of topical formulations and enhancing their efficacy.
6) Gene Delivery and Therapy: Microneedles can facilitate the delivery of genetic material, such as DNA or RNA, into target cells for gene therapy applications. By delivering therapeutic genes directly into the skin or underlying tissue, microneedles offer a potential approach for treating genetic disorders, cancer, and other diseases.
7) Research and Biotechnology: Microneedles are valuable tools for biomedical research, offering precise control over drug delivery and cellular manipulation. They are used in applications such as studying skin physiology, investigating drug permeation mechanisms, and developing novel therapeutic strategies.
8) These applications highlight the versatility and potential impact of microneedle technology in advancing healthcare, diagnostics, and biotechnology, offering minimally invasive solutions for drug delivery, monitoring, and therapy.

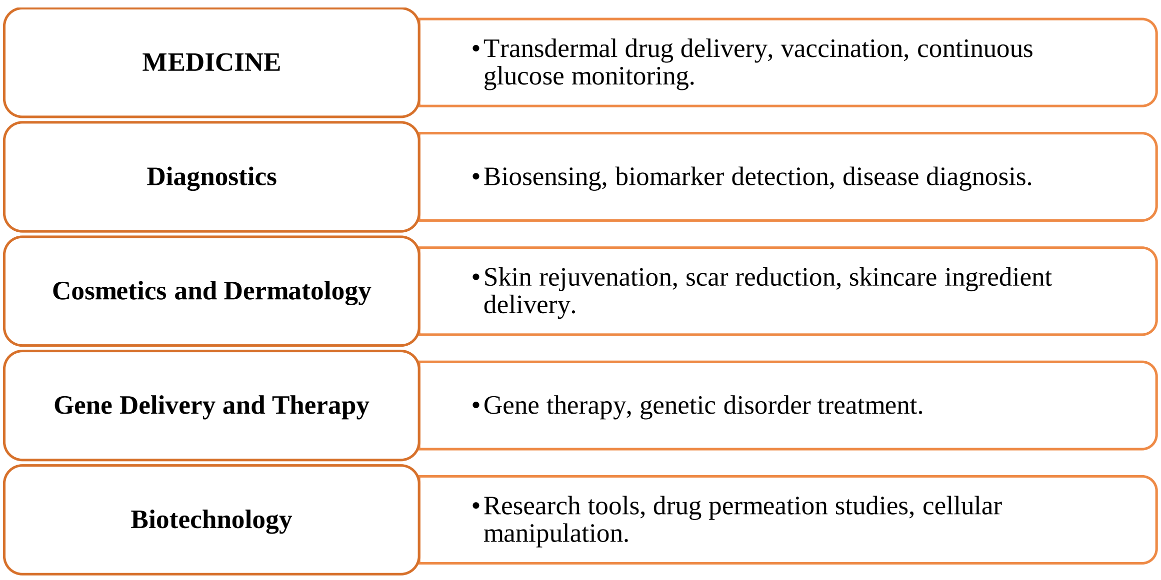


**figure : 5 application of microneedles**

## ➢ FUTURE PROSPECT

The future of microneedle drug delivery looks promising with advancements in drug delivery efficiency, personalized medicine, combination therapies, integrated diagnostics and therapy, remote self-administration, sustained release formulations, and expanded therapeutic applications. These developments hold the potential to revolutionize healthcare by offering safer, more effective, and patient-centric treatment options for various diseases and conditions.

## ➢ Conclusion

In conclusion, micro needle technology holds significant promise for enhancing transdermal and intradermal drug delivery by overcoming the stratum corneum barrier. This paper provides a comprehensive overview of micro needle technology in the context of transdermal drug delivery, highlighting various design types, materials, and manufacturing methods. Recent investigations demonstrate the potential of micro needle systems to efficiently deliver small molecular drugs, salt forms, excipients, and macromolecules such as therapeutic peptides, proteins, and vaccines. However, despite advancements in micro needle -mediated drug delivery, there remains a gap in cost-effective manufacturing for large-volume production. Addressing this gap is essential for realizing the full potential of micro needle technology in revolutionizing drug delivery and advancing medical treatment.

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